REMARKS

The Claims

Claims 21-31 are currently pending in the application. Claim amendments have been made after final rejection solely to adopt examiner suggestions, and place the claims in condition for allowance or in better form for appeal. The amendments do not introduce new matter or raise issues requiring further consideration and/or search. Entry of the amendments is respectfully requested.

Claim objections

Claim 22 has been objected to for failing to reference a sequence ID number after the term "Figure 1" in line 3 of the claim. The claim has been corrected to include the sequence ID number.

Rejection under 35 U.S.C. 112

Claims 21-31 stand rejected under 35 U.S.C. 112, first paragraph, as it is alleged that undue experimentation would be required to use the claimed OPG variants and fragments. The Examiner argues that there is no requirement for biological activity in the claims and therefore the claims would encompass inactive OPG polypeptides and fusion proteins thereof.

Without acquiescing to the rejection and solely to advance prosecution, Applicants have amended Claim 21 to recite that the claimed fusion proteins have the activity of decreasing bone resorption. The amendment has been made solely to clarify the activity of the fusion proteins and does not narrow the scope of the subject matter claimed therein.

Rejection under 35 U.S.C. 102

Claims 21 and 23 stand rejected under 35 U.S.C. 102(b) as being anticipated by Boyle et al. (PCT publication no. WO97/23614 cited by Applicants). The Examiner argues that Boyle et al. teach a fusion protein comprising an OPG variant 22-401 fused at its N-terminus to the C-terminus of the Fc protein (citing p. 105, lines 19-25 of the Boyle et al. reference) thereby anticipating the claims.

Without acquiescing to the rejection, Applicants have amended Claim 21 to recite a protein comprising a variant or fragment of OPG, wherein OPG comprises amino acids 22-401 as shown in Figure 2 (SEQ ID NO:2). The amendment was made solely to clarify that the

claimed variants or fragments differ from OPG comprising residues 22-401 and does not narrow the scope of the claims. It is requested that the rejection of Claim 21 be withdrawn.

As to Claim 23, the Examiner has not provided any reasons why the disclosure of WO97/23614 anticipates the subject matter of the claim. All of the proteins recited in Claim 23 are different from OPG [22-401] fused at its N-terminus to the C-terminus of the Fc protein. The Examiner has not pointed to any subject matter in Claim 23 that would be anticipated by the Boyle et al. reference. It is requested that the rejection of Claim 23 be withdrawn.

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Rejection under 35 U.S.C. 103(a)

Claims 21-31 are rejected under 35 U.S.C. 103(a) as being obvious over Mann et al. (PCT publication no. 98/28427 cited by Applicants) in view of U.S. Patent No. 6,015,938 to Boyle et al (hereafter the "'938 patent"). The Examiner argues that Mann et al. "clearly teaches the advantages of fusion of the Fc at the N-terminus to the protein which demonstrated advantages of stability, clearance rate and decreased degradation which was not seen in the fusion protein of the Fc to the C-terminus of the protein (see page 4, lines 15-35)". The Examiner further argues that the advantages of the Fc fusions taught by Mann together with the disclosure of OPG in the '938 patent would lead one skilled in the art to make an Fc fusion to N-terminus of OPG. Applicants disagree.

Applicants reiterate their previous arguments, namely that the Examiner has not pointed to a suggestion or motivation in the references to make Fc-OPG fusion proteins. The Examiner's arguments, at best, provide only an invitation to try and make any Fc fusion protein, with no motivation to make an Fc-OPG polypeptide.

Moreover, Applicants maintain that the advantages of Fc-OPG polypeptides compared to unfused OPG would not have been expected. The demonstration of advantageous properties by an Fc fusion protein can depend upon a number of factors One important factor is that the activity of the protein fused to Fc must be retained. Fusions of Fc to the N-terminus of a protein can disrupt the activity of the protein when, for example, the N-terminus of the protein is important for activity. In that instance, any advantages resulting from improved stability, longer clearance rates, and decreased degradation would not be apparent in the fusion protein.

While Mann et al. successfully made Fc-OB fusion proteins (Fc linked to the N-terminus of the OB protein) with improved properties, there were no teachings in the art that would have led one skilled in the art to be certain that such an Fc fusion to OPG would also have improved properties. For example, PCT publication no. WO97/23614 discloses that carboxy-terminal truncated forms of OPG retain biological activity suggesting that it may be possible to make Fc

fusions at the carboxy-terminus of OPG and still retain biological activity of OPG. Such biologically active OPG-Fc fusions (Fc fused to the carboxy-terminus of OPG) were in fact disclosed in WO97/23614. However, there was no assurance that an Fc fusion at the amino terminus would even result in an active polypeptide, let alone one which has advantageous properties compared to an unfused OPG polypeptide. Thus, the results obtained in Tables 3 and 4 of the present specification showing increased *in vivo* activity of Fc-OPG fusions compared to unfused OPG polypeptides are unexpected.

In conclusion, the claimed invention is nonobvious and it is requested that the rejection be withdrawn.

CONCLUSION

Claims 21-31 are in condition for allowance and an early notice thereof is solicited.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

21. (amended) A protein having a formula selected from the group consisting of R_1-R_2 and R_1-L-R_2, wherein R_1 is a Fc protein, or a variant or fragment thereof, R_2 is a variant or fragment of an osteoprotegerin (OPG) protein comprising amino acids 22-401 as shown in Figure 2 (SEQ ID NO:2) [variant or fragment], and L is a linker, wherein the protein has the activity of decreasing bone resorption.

22. (amended) The protein according to claim 21, wherein the Fc protein is selected from the group consisting of:

(a) the Fc amino acid sequences as set forth in Figure 1 (SEQ ID NO:1);

(b) the amino acid sequence of subpart (a) having a different amino acid substituted or deleted in one or more of the following positions (using the numbering according to Figure 1 (SEQ ID NO:1)):

(i) one or more cysteine residues;

(ii) one or more tyrosine residues;

(iii) cysteine at position 5 deleted or substituted with an alanine;

(iv) leucine at position 20 deleted or substituted with glutamine;

(v) glutamic acid at position 103 deleted or substituted with an alanine;

(vi) lysine at position 105 deleted or substituted with an alanine;

(vii) lysine at position 107 deleted or substituted with an alanine;

(viii) deletion or substitution of one or more of the amino acids at positions 1, 2, 3, 4, and 5;

(ix) one or more residues substituted or deleted to ablate the Fc receptor binding site;

(x) one or more residues substituted or deleted to ablate the complement (C1q) binding site; and

(xi) a combination of subparts i-x;

(c) the amino acid sequence of subparts (a) or (b) having a methionyl residue at the N-terminus;

(d) the Fc protein, or variant, fragment or derivative thereof, of any of subparts (a) through (c) comprised of a chemical moiety connected to the protein moiety;

(e) a derivative of subpart (d) wherein said chemical moiety is a water soluble polymer moiety;

(f) a derivative of subpart (e) wherein said water soluble polymer moiety is polyethylene glycol; and

(g) a derivative of subpart (e) wherein said water soluble polymer moiety is attached at solely the N-terminus of said protein moiety.